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Genetic biomarkers in the over 40s in Northern Ireland: evidence from the Northern Ireland COhort of Longitudinal study of Ageing (NICOLA)

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INTRODUCTION

The Northern Ireland COhort of Longitudinal study of Ageing (NICOLA) is a population-based prospective cohort study, formally launched as Northern Ireland's largest ever public health research project in 2014, and representative of the community living older population (>40 years) in Northern Ireland.

Chronic kidney disease (CKD) is an important public health problem affecting up to 10% of adults worldwide. CKD and classic polygenic traits as lipid levels and anthropomorphic traits are highly heritable, with many common associated variants identified through genome-wide association (GWA) studies.

OBJECTIVE

The aim of this study is to identify biomarkers associated with CKD, lipid levels and anthropomorphic traits in older adults in Northern Ireland and to describe a genomic profile of this population.

METHODOLOGY

This is a cross-sectional study using biomolecular and clinical data from 2,807 patients from the first Wave of data collection in NICOLA. Demographic and clinical information was collected with follow-up interviews planned every two years and health assessments every four years. A range of phenotypes was investigated: CKD (estimated glomerular filtration rate (eGFR), creatinine, cystatin C, CKD stage), lipid levels (total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels), anthropomorphic traits (height, body mass index, waist-hip ratio).

DNA was extracted from buffy coats. Genotype data (n=551,839 markers) was generated using Illumina's Infinium CoreExome-24 BeadChips for high-throughput screening on an iScan. Quality control (QC) was performed in PLINK and association analysis (logistic or linear regression) in PLINK and R/SPSS.

RESULTS

Phenotype measures were obtained for 2,529 (kidney measures), 2,543 (lipid levels), and 2,488 (anthropomorphic traits) individuals after QC (Table 1). Age and sex were employed as covariates. Several markers in chromosomes 11, 16, and 19 were significantly associated with lipid levels in this population (Table 2). No association with genome-wide significance was identified for kidney disease or anthropomorphic traits.

	Phenotypes	n	mean	Standard deviation	median	minimum	maximum
Anthropomorphic Traits	Age (yrs)	2541	64.16	9.28	64.00	40.00	96.00
	Body Masss Index (kg/m²)	2530	28.77	5.03	28.04	16.15	67.44
	Weight (kg)	2530	79.47	16.27	78.00	39.40	174.80
	Height (cm)	2534	165.97	9.27	165.75	141.00	199.00
	Waist Circumference (cm)	2523	95.45	13.88	94.90	38.00	157.40
	Hip (cm)	2523	104.68	9.47	103.40	47.50	181.95
	Waist-Hip Ratio	2523	0.91	0.09	0.91	0.67	1.20
Lipid Levels	Age (yrs)	2484	64.13	9.26	64.00	40.00	96.00
	Total Cholesterol (mg/dL)	2488	199.32	45.07	198.74	78.15	391.72
	LDL-Cholesterol (mg/dL)	2431	111.49	38.31	110.59	6.99	279.87
	HDL-Cholesterol (mg/dL)	2485	57.9	15.4	55.9	12.9	129.5
	Triglycerides (mg/dL)	2488	152.67	88.21	133.92	21.34	878.70
Kidney Measures	Age (yrs)	2529	64.15	9.26	64.00	40.00	93.00
	Creatinine (mg/dl)	2528	0.89	0.28	0.83	0.53	7.39
	eGFR (EPI)	2529	80.87	15.84	83.91	4.99	118.09
	CKD stage	N	%				
	1	825	32.70				
	2	1425	56.35				
	3A	199	7.87				
	3B	65	2.57				
	4	11	0.43				
	5	2	0.08				

CKD: Chronic Kidney Disease; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Table 1. Clinical characteristics of the NICOLA participants

	Chr	Gene Variant	Gene	BETA	P-value
Total Cholesterol	19	rs7412	APOE	-13.62	5.34E-10
High Density Cholesterol	16	rs9989419	CETP	-2.41	3.90E-09
	16	rs173539	CETP	3.48	2.19E-15
	16	rs247616	CETP	3.45	6.28E-15
	16	rs247617	CETP	3.45	6.28E-15
	16	rs183130	CETP	3.47	4.63E-15
	16	rs3764261	CETP	3.47	4.59E-15
	16	rs1800775	CETP	3.16	4.57E-15
	16	rs9939224	CETP	-3.75	5.43E-15
	16	rs7205804	CETP	3.16	2.15E-14
	16	rs1532624	CETP	3.23	4.61E-15
	16	rs7499892	CETP	-4.18	4.96E-16
	16	exm1242986	CETP	-5.22	2.13E-10
Low Density Cholesterol	19	rs7412	APOE	-16.21	1.49E-17
	19	rs445925	APOE	-10.23	1.57E-09
Triglycerides	11	rs964184	ZPR1	23.50	9.46E-10
	19	rs7412	APOE	-13.98	1.34E-11

Table 2. Association of gene variants with lipid levels

DISCUSSION

Some of the markers identified in this study in older individuals confirm previous associations with lipid levels in other populations. Despite multiple loci being identified in association with eGFR and CKD in both European and non-European populations, those were not replicated in this study, likely as a consequence of the relatively small number of individuals investigated in NICOLA with this phenotype.